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Abstract: Sex differences in response to experimental pain are commonly reported in systematic reviews in the adult literature. The objective of the present research was to conduct a systematic review and meta-analysis of sex differences in healthy children's responses to experimental pain (e.g., cold pressor, heat pain, pressure pain) and, where possible, to conduct analyses separately for children and adolescents. A search was conducted of electronic databases for published papers in English of empirical research using experimental pain tasks to examine pain-related outcomes in healthy boys and girls between 0 and 18 years of age. Eighty articles were eligible for inclusion and were coded to extract information relevant to sex differences. The systematic review indicated that, across different experimental pain tasks, the majority of studies reported no significant differences between boys and girls on pain-related outcomes. However, the meta-analysis of available combined data found that girls reported significantly higher pain intensity compared to boys in studies where the mean age of participants was greater than 12 years. Additionally, a meta-analysis of heat pain found that boys had significiantly higher tolerance than girls overall, and boys had significantly higher heat pain threshold than girls in studies where the mean age of participants was 12 years or younger. These findings suggest that developmental stage may be relevant for understanding sex differences in pain.

*Abstract

SEX DIFFERENCES IN EXPERIMENTAL PAIN IN CHILDREN

Abstract

Sex differences in response to experimental pain are commonly reported in systematic reviews in the adult literature. The objective of the present research was to conduct a systematic review and meta-analysis of sex differences in healthy children's responses to experimental pain (e.g., cold pressor, heat pain, pressure pain) and, where possible, to conduct analyses separately for children and adolescents. A search was conducted of electronic databases for published papers in English of empirical research using experimental pain tasks to examine pain-related outcomes in healthy boys and girls between 0 and 18 years of age. Eighty articles were eligible for inclusion and were coded to extract information relevant to sex differences. The systematic review indicated that, across different experimental pain tasks, the majority of studies reported no significant differences between boys and girls on pain-related outcomes. However, the meta-analysis of available combined data found that girls reported significantly higher pain intensity compared to boys in studies where the mean age of participants was greater than 12 years. Additionally, a meta-analysis of heat pain found that boys had significiantly higher tolerance than girls overall, and boys had significantly higher heat pain threshold than girls in studies where the mean age of participants was 12 years or younger. These findings suggest that developmental stage may be relevant for understanding sex differences in pain.

Keywords: sex differences; experimental pain; children; meta-analysis

Sex differences in experimental pain among healthy children: A systematic review and meta-analysis

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Sex differences in experimental pain among healthy children:

A systematic review and meta-analysis

Sex differences represent a rapidly growing body of literature in the areas of biology, medicine, and neuroscience, as researchers attempt to illuminate the mechanisms that underlie differences between men and women [14]. According to the World Health Organization, sex refers to the biological and physiological distinctions between women and men.This can be contrasted with gender, which is defined as a psychosocial construct that embodies the attributes, behaviours, and roles that a given society considers to be acceptable for men and women [116].

Sex differences are commonly reported in adult pain, with numerous reviews providing evidence of greater prevalence rates of acute and chronic pain among women, with women also demonstrating greater sensitivity to experimental pain tasks, though the strength of this effect differs between pain modalities, outcome measures, and time points, and is considered to be a controversial phenomena [37,73,87]. The abundance of literature on adult sex differences in pain has allowed researchers to explore mechanisms through which pain differs in men and women, including both biological and psychosocial mechanisms [27,37,56,86]. Such research has important implications with regards to the assessment and treatment of pain in adults, such as recent advances in theories of "personalized pain management" through research on the differential analgesic responding of men and women [80]. Due to developmental factors it is inappropriate to generalize adult findings to pediatric populations, and the literature on sex differences in children's pain is comparatively sparse.

Epidemiological studies of chronic pain in childhood suggest that prevalence of chronic pain is greatest among adolescent girls, with the emergence of sex differences in chronic pain conditions seen around the time of pubertal development [58]. These findings are concordant with speculation from the adult literature that sex hormones are one of the mechanisms through which sex differences in pain perception and responding are explained [4,43]. Given the complexity of the numerous factors implicated in the development of chronic pain, a systematic review of research on sex differences in healthy children's pain is needed to fully understand and explore potential mechanisms. Experimental pain provides a starting point for such examinations, controlling for many of the confounding factors that complicate interpretations of results in studies of clinical pain. Prior reviews have only provided narrative descriptions of select studies of sex differences in experimental pain among children and adolescents [55,77]. The primary objectives of the present study were to: (1) systematically review the existing literature on sex differences in responses to experimental pain in healthy children, and (2) meta-analyze data from published studies on experimental pain in boys and girls to provide a further investigation of sex differences beyond those statistics reported in published articles. Additionally, where possible, meta-analyses were to be conducted separately for children (participant mean age less than 12 years) and adolescents (participant mean age of 12 years or older). Finally, an additional objective was to examine the reporting practices of sex and gender in the studies included in the review.

Methods

Search method

A search was conducted of key electronic databases (PsycINFO, EMBASE, CINAHL, PubMed) from the inception of databases throughNovember 2012. The basic structure of the search strategy was as follows: [((pediatric) OR child) OR adolescent] AND [pain] AND [(((((((experimental pain) OR cold pressor) OR quantitative sensory test) OR water load) OR heat pain) OR thermal pain) OR pressure pain) OR exercise task], searching primarily titles and abstracts of these key databases, using truncations as appropriate for the database (e.g., child*, adolescen*, quantitative sensory test*). Keywords were chosen to capture the population age range of interest, studies that included pain as an outcome, and to focus the search specifically on studies including an experimental pain task.

Eligibility criteria

Eligibility criteria required that included articles be: (1) An empirical investigation using an experimental pain task to examine pain-related outcomes (pain intensity, pain tolerance, pain threshold, pain affect, facial activity in response to pain, or physiological responses to pain); (2) Published in manuscript form in English; (3) Studies using community/healthy samples of children between 0 and 18 years of age only (or a healthy control group included in studies of clinical populations); (4) Studies that included both boys and girls. Experimental pain tasks were defined as any task that was intended to induce pain for which a pain-related outcome was measured.

Screening for eligibility, coding, and requests for missing data

The initial search revealed 519 unique abstracts, once duplicates were removed. Each abstract was reviewed by two co-authors (K.E.B. and K.A.B.) to determine eligibility. If eligibility could not be determined from the abstract, the full article was examined. A total of 440 abstracts were excluded for the following primary reasons: participants did not complete an experimental pain task (*n*=33, 7.5%), the study did not measure any pain-related outcomes (*n*=8, 1.8%), the abstract was not published in manuscript form (e.g., dissertations, book chapters, conference abstracts, *n*=46, 10.5%), the article was not published in English (*n*=8, 1.8%), the study was conducted with a clinical sample and did not include a healthy control group (*n*=69, 15.7%), the study included individuals outside of the 0-18 years of age range (*n*=254, 57.7%), the study sample was composed of only boys or only girls (*n*=8, 1.8%), the study was conducted with animals (*n*=14, 3.2%).

Therefore, from the initial search, 79 articles were identified as being eligible. Each of the 79 articles were read and data was extracted by a study author (K.E.B., K.A.B., L.C., or M.S.) using an author-created coding form that documented sample characteristics, details of the experimental pain tasks performed, and details related to any pain-related outcomes measured (including mean and standard deviation of the pain outcome for both boys and girls, as well as the results of any statistical tests conducted to examine sex differences). During coding, three additional articles were identified as being eligible for inclusion, as they were referenced in the paper as reporting on additional results from the same study sample [82,102,108]. These three articles were also coded and included in the study, resulting in a total of 82 articles coded for inclusion. See Figure 1 for a study flowchart employing the PRISMA model[74].

Coding sheets were examined to identify missing data. Authors were contacted and asked to supply data for any article that did not include the following: age range of participants, mean age of participants, mean and standard deviation for boys and girls separately for any pain outcome. When applicable, data was requested for baseline/control experimental pain tasks (i.e., tasks that did not involve an intervention or experimental manipulation) and for healthy/community samples only. Two attempts were made to contact the corresponding author of each paper where data was missing. Based on author responses, two articles that had originally been included in the review [11,103]were excluded, as it was revealed that the sample fell outside of the 0-18 year old age range. This resulted in a final total of 80 articles included, reporting on 81 separate studies, as one article reported on two studies with separate samples [109].

Overlapping samples

Every attempt was made to avoid the inclusion of overlapping samples in the review, as this would involve an over-representation of a subset of children. If it was unclear whether samples were overlapping, authors were emailed to confirm this information. Where it was known that samples were overlapping (i.e., >1 study included in the review that reported on the same sample of children), the authors of the present review went back to the first published study from that sample and worked forward chronologically through multiple publications reporting on the same sample of children, making note of outcomes the first time that full data was reported (e.g., means and standard deviations of pain outcome for boys and girls separately, and statistics regarding sex differences). If full data was not available from any of the studies involved in the overlapping sample, the authors were contacted and asked to provide data about the first chronological incidence of reporting. Where it was unclear whether samples were overlapping, the authors were contacted and asked to indicate whether multiple publications reported on the same sample of children. If authors did not respond, the studies were assumed to represent different samples of children and were treated as such in the review.

Data Analytic Approach

Information from data extraction coding sheets were entered into SPSS 20, and information from the systematic review was summarized using descriptive statistics. Due to the low number of studies included in the systematic review, results were combined across different experimental pain tasks.Sufficient data was available to conduct meta-analyses separately for cold pressor pain, heat pain, and pressure pain. Data needed to be available from at least two studies to conduct a meta-analysis for a particular pain outcome. All data suitable for pooling was analyzedwith RevMan 5.2 software using a fixed-effects analysis (unless otherwise indicated), as heterogeneity across studies was not observed or was low for each outcome [95]. Heterogneity was calculated using the I^2 statistic, with 0-40% interpreted as heterogeneity that might not be important, 30-60% taken as moderate heterogeneity, and 75-100% representing considerable heterogeneity [48]. For each study, the standardized mean difference and a 95% confidence interval was calculated. In studies where the same pain task was administered more than one time and the results of each trial were reported separately (or when the same pain outcome was measured more than one time within a pain task and data was reported for each time point), only data from the first trial/measurement was included. Note that when the same pain task was administered under different conditions but the order was counterbalanced across participants [76], a pooled mean was taken of pain outcomes across both conditions, as it could not be determined which pain task was administered first for each participant. The following formulas were used to pool means and SDs: pooled mean= [(mean1 x N1) + (mean2 x N2) / (N1 + N2)] and pooled SD =square root of [($SD1^2$)(N1-1) + ($SD2^2$)(N2-1)] / N1 + N2 -2. A pooled mean was also calculated for studies that reported results of the same pain task performed at multiple body locations (e.g., pressure pain measured at the neck and shoulder).

Given that many studies of sex differences in adult pain have speculated about the role of sex hormones in the development of sex differences in pain, the meta-analysis was also conducted separately for studies in which the mean age of participants was greater than or equal to 12 years of age, and those studies in which the mean age of participants was less than 12 years of age. This age was chosen as the cut-off as it represents the age at which many girls and boys have entered puberty, and as such (in the absence of measures of pubertal status) provides a proxy for the emergence of sex hormones[83]. Note that this approach was only taken for cases in which data was available for at least two studies in each age group. If the mean age of participants was not available because it was not reported or because the data suitable for pooling was from a subset of participants rather than the entire sample, categorization was determined by the age range of participants or the mean age of participants in the entire sample.

Results

Published accounts of sex differences in pain outcomes

Results of the systematic review are presented for each pain outcome measure summarized across experimental pain tasks. Note that several studies (*n*=25, 30.9%) had children complete more than one different type of experimental pain task, and results from statistical tests of sex differences were included for each unique pain task, even if it was performed on the same sample of children.Tables 1 through 4 provide the results of the systematic review separately by experimental pain induction method. Note that the following studies eligible for inclusion in the systematic review conducted additional experimental pain tasks (e.g., fabric prickliness test, ischemic pain, brush allodynia, manual palpation, dynamic mechanical allodynia, tactile pain sensitivity) but did not conduct statistical tests examining sex differences in healthy children and therefore are not included in Tables 1-4: [6,18,49,89,111,115].

Pain intensity. Of the pain tasks where it was reported that statistical tests of sex differences in pain intensity were conducted (*n*=21 pain tasks from 18 unique studies), 90.5% reported no sex differences, and 9.5% indicated girls reported significantly higher levels of pain intensity than boys.

Pain threshold. Of the pain tasks where it was reported that statistical tests of sex differences in pain thresholdwere conducted (*n*=16 pain tasks from 9 unique studies), 68.8%

reported no sex differences, and 31.2% indicated that boys had a significantly higher pain threshold than girls.

Pain tolerance. Of the pain tasks where it was reported that statistical tests of sex differences in pain tolerancewere conducted (*n*=16 pain tasks from 16 unique studies), 75% reported no sex differences, 12.5% indicated that girls had a higher pain tolerance than boys, and 12.5% indicated that boys had a higher pain tolerance than girls.

Pain affect. Of the pain tasks where it was reported that statistical tests of sex differences in pain affect were conducted (*n*=7 pain tasks from 5 unique studies), 85.7% reported no sex differences, and 14.3% indicated that girls reported greater pain affect than boys in response to an experimental pain task.

Facial activity in response to pain. Of the pain tasks where it was reported that statistical tests of sex differences in facial activity in response to pain were conducted (*n*=8 pain tasks from 8 unique studies), 75% reported no sex differences, and 25% indicated that boys displayed greater facial activity in response to pain than girls.

Physiological responses to pain. Of the pain tasks where it was reported that statistical tests of sex differences in physiological responses to pain were conducted (*n*=6 pain tasks reporting on 9 measures of physiological responses from 4 unique studies[1]), 88.8% reported no sex differences, and 11.1% indicated that boys had a greater physiological response (blood pressure) to pain than girls.

Meta-analysis of sex differences in cold pressor pain

[1]Note that one of the studies required children to participate in >1 experimental pain task ([78]: CPT, heat pain, pressure pain) and measured two physiological responses (salivary and blood cortisol) after the completion of all three tasks. Additionally, another included study measured physiological responses to cold pressor pain with multiple modalities ([38]: physiological responses measured using heart rate, skin conductance, respiratory rate, EMG, blood pressure, and skin temperature). Results from statistical tests of sex differences were included for each unique pain task and physiological response measure, even if it was performed on the same sample of children.

When full data was not available in the published manuscript, authors were contacted and requested to provide data for the meta-analytic portion of this research. Of the 49 requests for data sent, 9 responses (18.4%) were received indicating that the data was not available, and 27 responses (55.1%) provided additional data. When this was combined with the data available from published mansucripts, data for meta-analysis was available from 33 separate samples, with a combined total of 2109 unique participants (1069 girls and 1040 boys).

Pain intensity. Data from 19 studies (published in 18 separate articles) were entered into the meta-analysis, which compared self-reported pain intensityduring the cold pressor taskin a total of 628 girls and 633 boys [16,26,39,40,54,75,76,78,82,84,85,93,94,96,99,105,106,109]. Pain intensity was measured using a variety of self-report tools, including the Faces Pain Scale (original [7] and revised [47]versions), numerical rating scales, visual analogue scales, and the Coloured Analogue Scale [66]. This analysis revealed a standardized mean difference (SMD) of 0.10 [-0.01, 0.21] and an I^2 of 0%, indicating no observed heterogeneity. While the mean self-reported pain intensity of girls was greater than boys, this effect was not significant ($Z = 1.76$, $p = .08$).

The meta-analysis was repeated to separately examine studies for which the mean age of participants was greater/equal to or less than 12 years of age. For studies with a mean age of less than 12 years, data from 12 studies were entered into the meta-analysis, with a total of 302 girls and 303 boys [16,26,39,54,75,76,82,84,85,93,96,99]. This analysis revealed a SMD of 0.01 [-0.15, 0.17], an I^2 of 0%, and no signficant differences between boys and girls on self-reported pain intensity ($Z= 0.08$, $p = .93$).

However, a significant effect was present in the studies with a mean age of equal to or greater than 12 years, in which seven studies (from six published articles) were entered into the meta-analysis, with a total of 321 girls and 330 boys [40,78,94,105,106,109]. This analysis revealed a SMD of 0.19 [0.03, 0.34], an I^2 of 33%, and a significant difference in which girls reported significantly greater pain intensity in response to the cold pressor task than boys (Z = 2.35, p = .02).

Pain threshold. Data from six studies were entered into the meta-analysis, which compared pain threshold in a total of 154 girls and 149 boys [23-25,93,94,96]. This analysis revealed a SMD of 0.12 [-0.11, 0.35] and an I^2 of 15%, indicating low heterogeneity. This effect was not significant (Z = 1.02, p = .31), indicating no significant differences in pain threshold during the cold pressor task between boys and girls. As all but one study had a mean age less than 12 years old, the meta-analysis was not conducted separately for different age groups.

Pain tolerance. Data from 18 studies (published in 17 separate articles) were entered into the meta-analysis, which compared pain tolerance in a total of 628 girls and 600 boys [16,23-26,54,60,76,78,84,85,93,94,96,99,109,113]. This analysis revealed a SMD of 0.04 [-0.07, 0.16] and an I^2 of 0%, indicating no observed heterogeneity. This effect was not significant (Z = 0.72, p = .47), indicating no difference between boys and girls on pain tolerance during the cold pressor task.

The meta-analysis was repeated to separately examine studies for which the mean age of participants was greater/equal to or less than 12 years of age. For studies with a mean age of less than 12 years, data from 14 studies were entered into the meta-analysis, with a total of 366 girls and 342 boys [16,23-26,54,60,76,84,85,93,96,99,113]. This analysis revealed a SMD of 0.07 [-0.08, 0.22], an I^2 of 0%, and no signficant differences between boys and girls on pain tolerance during the cold pressor task (Z= 0.93, p = .35).

Similar results were seen in the meta-analysis of studies in which participant mean age was greater than 12 years, in which four studies (from three published articles) were included, with a total of 262 girls and 258 boys [78,94,109]. This analysis revealed a SMD of 0.00 [-0.17, 0.18], an I^2 of 0%, and no signficant differences between boys and girls on pain tolerance during the cold pressor task (Z= 0.03, p = .98).

Pain affect. Data from nine studies were entered into the meta-analysis, which compared self-reported pain affect in a total of 308 girls and 327 boys [16,61,76,78,82,93,94,96,104]. Pain affect was measured usingseveral self-report tools, including the Facial Affective Scale [65], the Children's Fear Scale [67], and numerical rating scales and visual analogue scales for "pain discomfort" or "pain unpleasantness." This analysis revealed a SMD of 0.02 [-0.13, 0.18] and an I^2 of 0%, indicating no observed heterogeneity. This effect was not significant (Z = 0.29, p = .77), indicating no difference between boys and girls on self-reported pain affect during the cold pressor task.

The meta-analysis was repeated to separately examine studies for which the mean age of participants was greater/equal to or less than 12 years of age. For studies with a mean age of less than 12 years, data from six studies were entered into the meta-analysis, with a total of 183 girls and 207 boys [16,61,76,82,93,96]. This analysis revealed a SMD of 0.02 [-0.13, 0.18], an I^2 of 0%, and no signficant differences between boys and girls on pain affect during the cold pressor task (Z= 0.29, p = .77).

Similar results were seen in the meta-analysis of studies in which participant mean age was greater than 12 years, in which three studies were included, with a total of 125 girls and 120 boys [78,94,104]. This analysis revealed a SMD of 0.08 [-0.17, 0.33], an I^2 of 0%, and no signficant differences between boys and girls on pain affect during the cold pressor task (Z= 0.65, p = .52).

Facial expression of pain. Data from six studies were entered into the meta-analysis, which compared facial expressions of pain in a total of 118 girls and 127 boys [16,40,59,75,105,106]. Scores for facial expression in response to pain were coded in each study using the Child Facial Coding System [15] or the Facial Action Coding System [28] (note that how facial expression scores were calculated differed across studies in that some studies reported a score based on all facial action units, while others calculated a score based on only those facial action units that have been identified as corresponding to expressions of pain). This analysis revealed a SMD of 0.00 [-0.26, 0.25] and an I^2 of 0%, indicating no observedheterogeneity. This effect was not significant (Z = 0.03, p = .98), indicating no difference between boys and girls on facial expressions in response to the cold pressor task.

The meta-analysis was repeated to separately examine studies for which the mean age of participants was greater/equal to or less than 12 years of age. For studies with a mean age of less than 12 years, data from three studies were entered into the meta-analysis, with a total of 81 girls and 82 boys [16,59,75]. This analysis revealed a SMD of 0.08 [-0.22, 0.39], an I^2 of 0%, and no signficant differences between boys and girls in facial expressions in response to the cold pressor task (Z= 0.53, p = .60).

Similar results were seen in the meta-analysis of studies in which participant mean age was greater than 12 years, in which three studies were included, with a total of 62 girls and 70 boys [40,105,106]. This analysis revealed a SMD of 0.02 [-0.33, 0.36], an I^2 of 40%, and no signficant differences between boys and girls on facial expression in response to the cold pressor task (Z= 0.09, p = .93).

Physiological reaction. Data from four studies were entered into the meta-analysis, which compared physiological reactions to the cold pressor task in a total of 154 girls and 149 boys [16,26,39,75]. In each of the included studies, physiological reactions were measured using participant heart rate. This analysis revealed a SMD of 0.09 [-0.24, 0.41] and an I^2 of 0%, indicating no observed heterogeneity. This effect was not significant ($Z = 0.52$, $p = .60$), indicating no significant differences in heart rate in response to the cold pressor task between boys and girls. As all included studies had a mean age less than 12 years old, the meta-analysis was not conducted separately for different age groups.

Meta-analysis of sex differences in experimental heat pain

Meta-analyses were conducted for pain intensity, tolerance, and thershold for experimental heat pain. There was insufficient data available to conduct analyses for pain affect, facial expression, or physiological responses.

Pain intensity. Data from three studies were entered into the meta-analysis, which compared self-reported pain intensity in a total of 154 girls and 155 boys during experimental heat pain[13,39,78]. Pain intensity was measured using numerical rating scales and visual analogue scales. This analysis revealed a SMD of 0.07 [-0.15, 0.30] and an I^2 of 0%, indicating no observed heterogeneity. No significant differences between boys and girls on self-reported pain intensity during heat pain were observed ($Z = 0.63$, $p = .53$). As there were less than two studies in each age group, the meta-analysis was not conducted separately for different age groups.

Pain threshold. Data from three studies were entered into the meta-analysis, which compared pain threshold in a total of 179 girls and 183 boys [8,9,39]. This analysis revealed a SMD of -0.31 [-0.52,-0.11] and an I^2 of 0%, indicating no observed heterogeneity. This effect was significant ($Z = 2.96$, $p = .003$), indicating that boys had a significantly higher heat pain threshold than girls.

As two of the included studies reported means and standard deviations separately by age group, it was possible to conduct a meta-analysis to separately examine study samples for which the mean age of participants was greater/equal to or less than 12 years of age. For studies with a mean age of less than 12 years, data from three studies were entered into the meta-analysis, with a total of 104 girls and 107 boys [8,9,39]. This analysis revealed a SMD of -0.34 [-0.61,-0.07], an I^2 of 0%, and a significant difference in which boys had significantly higher heat pain threshold than girls ($Z = 2.46$, $p = .01$).

Similar results were seen in the meta-analysis of studies in which participant mean age was greater than 12 years, in which data fromtwo studies were included, with a total of 75 girls and 76 boys[8,9]. This analysis revealed a SMD of -0.27 [-0.60, 0.05], and an I^2 of 0%. While the mean pain threshold of boys was greater than the mean pain threshold of girls, this effect was not significant ($Z = 1.68$, $p = .09$).

Pain tolerance. Data from two studies were entered into the meta-analysis, which compared pain tolerance in a total of 152 girls and 148 boys[13,64]. Note that as heterogeneity was high in this comparison (I^2=91%) a random effects model was used. This analysis revealed a SMD of -1.26 [-2.29, -0.23] with a significant effect ($Z = 2.40$, $p = .02$), indicating that boys had significantly higher tolerance of heat pain than girls. As there were less than two studies in each age group, the meta-analysis was not conducted separately for different age groups.

Meta-analysis of sex differences in experimental pressure pain

Meta-analyses were conducted for pain intensity and threshold for experimental heat pain. There was insufficient data available to conduct analyses for pain tolerance, pain affect, facial expression, or physiological responses.

Pain intensity. Data from two studies were entered into the meta-analysis, which compared self-reported pain intensity in a total of 164 girls and 160 boysundergoing experimental pressure pain [78,107]. Pain intensity was measured using numerical rating scales and visual analogue scales. This analysis revealed a standardized mean difference (SMD) of 0.17 [-0.5, 0.39] and an I^2 of 0%, indicating no observed heterogeneity. No significant differences between boys and girls on self-reported pain intensity during pressure pain were observed (Z = 1.51, p = .13). As there were less than two studies in each age group, the meta-analysis was not conducted separately for different age groups.

Pain threshold. Data from two studies were entered into the meta-analysis, which compared pain threshold in a total of 81 girls and 62 boys [71,107]. Note that as heterogeneity was high in this comparison (I^2=78%) a random effects model was used. This analysis revealed a SMD of -0.35 [-1.08,0.39] and this effect was not significant (Z = 0.93, p = .35), indicating no significant differences in pain threshold during experimental pressure pain between boys and girls. As there were less than two studies in each age group, the meta-analysis was not conducted separately for different age groups.

Reporting practices of sex and gender variables

Of the 81 included studies, 41 studies (50.6%) had reported results of statistical tests examining sex differences for at least one pain-related outcome (note that this included studies that merely reported that sex differences were or were not present, even if the authors did not include numericalvalues of the statistical test conducted or the mean values of the different groups). Nine studies (11.1%) reported entering sex as a covariate in their analyses. Two studies (2.5%) reported using a validated measure of child gender (e.g., the *Children's Sex Role Inventory*[10]) to examine the relationship between child gender and pain outcomes [78,109].

With regards to terminology use, 36 studies (44.4%) used the appropriate terminology when referring to "sex" or "gender", according to the defitions of sex and gender set out by the World Health Organization [116]. Of the remaining studies, 29 studies (35.8%) used the term "gender" when grouping participants based on sex, 7 studies (8.6%) used the terms "sex" and "gender" interchangeably throughout the article, and 9 studies (11.1%) did not use either term at all.

Discussion

Systematic review and meta-analysis of sex differences

The results of this systematic review indicate that the majority of studies on children's responses to experimental pain report no significant sex differences on pain-related outcomes. However, the meta-analysis of cold pressor pain intensity revealed that girls reported significantly higher pain intensity than boys when pooling data from studies that had a mean age >12 years, an age typically associated with onset of pubertal development in both boys and girls[83]. While such an approach to examining age is crude, a more detailed analyses by age and/or pubertal status was not feasible with the information available. Nonetheless, this analysis offers preliminary support for the hypothesis that sex differences in experimental cold pressor pain, similar to chronic pain, emerge in adolescence and could possibly be related to the emergence of sex hormones [58]. This is in line with findings in other areas of research, in which the emergence of sex differences of other disorders and conditions (e.g., anxiety, depression) are seen at puberty [21,22,57]. A more explicit examination of the role of sex hormones and pubertal stages in the development of sex differences is needed to control for other factors that could be contibuting to sex differences in adolescents (e.g., different methodologies used in research groups that study children vs. adolescents).

A meta-analysis of sex differences in response to experimental heat pain revealed that boys had significantly higher pain threshold and pain tolerance than girls, with no significant differences in pain intensity. Unlike cold pressor pain, the sex difference in heat pain threshold was still significant in studies where children had a mean age of 12 years or lower. These results should be interepreted with caution, as heat pain is not often used among children, and as such, the meta-analysis may have not been adequately powered to accurately represent the strength of sex difference effects in heat pain in children, particularly when split by age group.

In adults, pressure pain produces the largest sex differences of all experimental pain tasks [88]. In the present meta-analysis, no sex differences were observed in experimental pressure pain. The small number of studies using heat and pressure pain limits the ability to draw conclusions regarding effects of different experimental pain tasks. Inspection of available results from the systematic review does not appear to support task-specific sex effects, though more research in this area is certainly needed. In particular, examination of possible sex differences in pain emerging at different developmental stages for different types of pain tasks are currently lacking in children [37,87].

Reporting practices of sex and gender

In recent years, organizations such as the International Association for the Study of Pain have increasingly encouraged researchers to consider sex and gender in their research and to use appropriate terminology [42]. Despite the majority of studies having a representative sample of both boys and girls, less than half of included studies reported tests of sex differences in pain-related outcomes. Only two of the 81 studies included in this review reported on measures of child gender and its relationship to pain outcomes. Additionally, despite increasing awareness of the distinction between sex and gender, use of terminology in reviewed articles was often inappropriate, with the most common issue being use of the term "gender" when referring to the categorical distinction between boys and girls. Appropriate reporting is critical for advancing our understanding of the role of these variables in pain.

Strengths, Limitations, & Future Directions

A strength of the present research was the use of a meta-analytic approach, which allowed for pooling of data to examine sex effects and including data from studies that otherwise were not powered to look at sex differences. Additionally, the excellent response rate of authors providing data allowed for a quantitative synthesis of a large number of studies beyond what is available in the published literature. With regards to limitations, any systematic review or meta-analysis is subject to methodological variability across studies. For example, measurement of pain outcomes occurred at different times (e.g., several studies examined pain intensity at the beginning of the pain task, while others examined worst pain upon task completion). Rules were implemented regarding data extraction to control this variability (e.g., only the first measure of pain intensity taken was used), however some methodological variability remained unavoidable (e.g., the first measure of pain intensity may have occurred at different times across studies) and may have impacted the findings [73]. While physiological measures of pain have been commonly reported in adult reviews of sex differences in experimental pain, these measures are often not specific to pain and should be interpreted with caution [37]. Finally, while the majority of meta-analyses conducted had low or no observed heterogeneity, observed heterogeneity was high for a few select analyses undertaken (heat pain tolerance and pressure pain threshold).

The division of the meta-analysis by mean age of participants has several limitations. While the mean age indicated whether the majority of children were under/over the age of 12 years, many of the studies would have included children and adolescents at various stages of pubertal development in both groups. As such, the presence of potential sex differences in those children who had undergone puberty may have been washed out because they were being considered along with pre-pubertal children. Previous research has had conflicting conclusions whether pubertal status or age is more important for understanding the development of sex differences in children's pain [62,90]. As pubertal status was only measured in two studies in the present review [3,64], age was used as a proxy, however, this was not ideal and future research is need to replicate our age-related findings.

The heterogeneity of methods in the included studies, as well as the wide age ranges precludes conclusive statements regarding the effects of sex on healthy children's pain experience. Future research will require studies explicitly designed to examine sex differences in various age groups across pubertal development (which may include measurement of pubertal stage and/or presence of sex hormones in addition to age). Such studies may require large samples to be able to detect the small sex difference effects presented in this review, which are similar to the small-medium effect sizes seen in adult reviews [37]. Overall, for the cold pressor task, all standardized mean difference scores were less than 0.2 (range: 0.0-0.19), indicating very small effect sizes[19]. Heat pain tasks showed more variability in effect sizes, from small for pain intensity and threshold (*SMD* = 0.07 and -0.31, respectively), to quite large for pain tolerance (*SMD* = -1.26).Pressure pain tasks demonstrated small effect sizes for pain intensity and threshold (*SMD* = 0.17 and -.035, respectively). Researchers may consider using the effect sizes from the present study in calculating sample sizes, should they wish to examine sex differences in their own research. While many of the studies included in the present review did not report significant sex differences, this may have been due to insufficient power to detect such effects. For example, a t-test comparing boys and girls with a significance level of .05 and power of 0.8 would require close to 400 participants in each group to detect a small effect size, which is much larger than the standard sample size for experimental pain studies. Schmitz and colleagues [90] recently demonstrated important future directions for the field through the inclusion of large sample sizes and methodology designed explicitly to examine sex differences across pubertal development. Researchers should consider conducting similar studies looking at additional pain outcomes (e.g., pain intensity) and using different experimental pain paradigms.

With regards to future research directions, it will also be important for investigators to continue examining the impact of gender on pain responses in childhood and adolescence. A recent meta-analysis of the impact of gender roles on experimental pain responses in adults supports the role of gender schema theory in influencing differential pain responding in men and women [1]. As gender schemas are known to be incorporated and understood by children at a young age, it will be important to examine the developmental trajectory of gender influences [79]. Sex differences in other psychosocial variables also deserve further investigation, such as children's pain coping styles and parental behaviour in response to pain. Finally, a similar systematic meta-analytic approach should be applied to clinical pain in children.

In summary, the majority of published accounts of sex differences in pain outcomes in healthy children reported no signficant differences between boys and girls on any pain outcomes. However, the meta-analysis of available combined data found that girls reported significantly higher increased pain intensity compared to boys in studies where the mean participant age was greater than 12 years. Additionally, a meta-analysis of heat pain found that boys had signficiantly higher tolerance than girls, and boys had significantly higher heat pain threshold than girls in studies where the mean participant age was 12 years or younger. Researchers should continue to include analyses of both sex and gender, as well as developmental factors such as puberty, to better understand how the sex differences observed in adult pain develop from childhood.

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References

[1] Alabas OA, Tashani OA, Tabasam G, Johnson MI. Gender role affects experimental pain responses: A systematic review with meta-analysis. European Journal of Pain 2012;16:1211-1223.

[2] Alfven G. The pressure pain threshold (PPT) of certain muscles in children suffering from recurrent abdominal pain of non-organic origin. An algometric study. Acta Paediatr 1993;82:481-483.

[3] Allen LB, Lu Q, Tsao JC, Worthman CM, Zeltzer LK. Sex differences in the association between cortisol concentrations and laboratory pain responses in healthy children. Gend Med 2009;6 Suppl 2:193-207.

[4] Aloisi AM, Bonifazi M. Sex hormones, central nervous system and pain. Horm Behav 2006;50:1-7.

[5] Anttila P, Metsähonkala L, Mikkelsson M, Aromaa M, Kautiainen H, Salminen J, Viander S, Jäppilä E, Sillanpää M. Muscle tenderness in pericranial and neck-shoulder region in children with headache. A controlled study. Cephalalgia 2002;22:340-344.

[6] Bar-Shalita T, Vatine J, Seltzer Z, Parush S. Psychophysical correlates in children with sensory modulation disorder (SMD). Physiol Behav 2009;98:631-639.

[7] Bieri D, Reeve RA, Champion GD, Addicoat L, Ziegler JB. The Faces Pain Scale for the self-assessment of the severity of pain experienced by children: Development, initial validation, and preliminary investigation for ratio scale properties. Pain 1990;41:139-150.

[8] Blankenburg M, Boekens H, Hechler T, Maier C, Krumova E, Scherens A, Magerl W, Aksu F, Zernikow B. Reference values for quantitative sensory testing in children and adolescents: Developmental and gender differences of somatosensory perception. Pain 2010;149:76-88.

[9] Blankenburg M, Meyer D, Hirschfeld G, Kraemer N, Hechler T, Aksu F, Krumova EK, Magerl W, Maier C, Zernikow B. Developmental and sex differences in somatosensory perception—A systematic comparison of 7- versus 14-year-olds using quantitative sensory testing. Pain 2011;152:2625-2631.

[10] Boldizar JP. Assessing sex typing and androgyny in children: The Children's Sex Role Inventory. Dev Psychol 1991;27:505-515.

[11] Bruehl S, Dengler-Crish CM, Smith CA, Walker LS. Hypoalgesia related to elevated resting blood pressure is absent in adolescents and young adults with a history of functional abdominal pain. Pain 2010;149:57-63.

[12] Caes L, Vervoort T, Eccleston C, Vandenhende M, Goubert L. Parental catastrophizing about child’s pain and its relationship with activity restriction: The mediating role of parental distress. Pain 2011;152:212-222.

[13] Caes L, Vervoort T, Trost Z, Goubert L. Impact of parental catastrophizing and contextual threat on parents' emotional and behavioral responses to their child's pain. Pain 2012;153:687-695.

[14] Cahill L. Why sex matters for neuroscience. Nature Reviews Neuroscience 2006;7:477-484.

[15] Chambers CT, Cassidy KL, McGrath PJ, Gilbert CA, Craig KD. Revised manual for the Child Facial Coding System. : Dalhousie University and University of British Columbia, 1996.

[16] Chambers CT, Craig KD, Bennett SM. The impact of maternal behavior on children's pain experiences: An experimental analysis. J Pediatr Psychol 2002;27:293-301.

[17] Chaves TC, Nagamine HM, de Sousa LM, de Oliveira AS, Grossi DB. Intra- and interrater agreement of pressure pain threshold for masticatory structures in children reporting orofacial pain related to temporomandibular disorders and symptom-free children. J Orofac Pain 2007;21:133-142.

[18] Chaves TC, Nagamine HM, de Sousa LM, de Oliveira AS, Grossi DB. Comparison between the reliability levels of manual palpation and pressure pain threshold in children who reported orofacial pain. Man Ther 2010;15:508-512.

[19] Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: Erlbaum, 1988.

[20] Coldwell SE, Kaakko T, Gärtner-Makihara AB, Williams T, Milgrom P, Weinstein P, Ramsay DS. Temporal information reduces children's pain reports during a multiple-trial cold pressor procedure. Behav Ther 2002;33:45-63.

[21] Conley CS, Rudolph KD. The emerging sex difference in adolescent depression: Interacting contributions of puberty and peer stress. Dev Psychopathol 2009;21:593-620.

[22] Craske MG. Origins of phobias and anxiety disorders: Why more women than men? Oxford, UK: Elsevier, 2003.

[23] Dahlquist LM, McKenna KD, Jones KK, Dillinger L, Weiss KE, Ackerman CS. Active and Passive Distraction Using a Head-Mounted Display Helmet: Effects on Cold Pressor Pain in Children. Health Psychol 2007;26:794-801.

[24] Dahlquist LM, Weiss KE, Clendaniel LD, Law EF, Ackerman CS, McKenna KD. Effects of videogame distraction using a virtual reality type head-mounted display helmet on cold pressor pain in children. J Pediatr Psychol 2009;34:574-584.

[25] Dahlquist LM, Weiss KE, Law EF, Sil S, Herbert LJ, Horn SB, Wohlheiter K, Ackerman CS. Effects of videogame distraction and a virtual reality type head-mounted display helmet on cold pressor pain in young elementary school-aged children. J Pediatr Psychol 2010;35:617-625.

[26] Dufton LM, Dunn MJ, Slosky LS, Compas BE. Self-reported and laboratory-based responses to stress in children with recurrent pain and anxiety. J Pediatr Psychol 2011;36:95-105.

[27] Edwards RR, Haythornthwaite JA, Sullivan MJ, Fillingim RB. Catastrophizing as a mediator of sex differences in pain: Differential effects for daily pain versus laboratory-induced pain. Pain 2004;111:335-341.

[28] Ekman P, Friesen W. Facial Action Coding System: A Technique for the Measurement of Facial Movement. Palo Alto, CA: Consulting Psychologists Press, 1978.

[29] Evans S, Lu Q, Tsao JC, Zelter LK. The Role of Coping and Race in Healthy Children's Experimental Pain Responses. J Pain Manag 2008;1:151-162.

[30] Evans S, Tsao JCI, Lu Q, Kim SC, Turk N, Myers CD, Zeltzer LK. Sex differences in the relationship between maternal negative life events and children's laboratory pain responsivity. J Dev Behav Pediatr 2009;30:279-288.

[31] Evans S, Tsao JCI, Zeltzer LK. Relationship of child perceptions of maternal pain to children's laboratory and nonlaboratory pain. Pain Res Manage 2008;13:211-218.

[32] Fanurik D, Zeltzer LK, Roberts MC, Blount RL. The relationship between children's coping styles and psychological interventions for cold pressor pain. Pain 1993;53:213-222.

[33] Fernandez-de-las-Penas C, Ambite-Quesada S, Rivas-Martinez I, Ortega-Santiago R, de-la-Llave-Rincon AI, Fernandez-Mayoralas DM, Pareja JA. Genetic contribution of catechol-O-methyltransferase polymorphism (Val158Met) in children with chronic tension-type headache. Pediatr Res 2011;70:395-399.

[34] Fernandez-De-Las-Penas C, Fernandez-Mayoralas DM, Ortega-Santiago R, Ambite-Quesada S, Gil-Crujera A, Fernandez-Jaen A. Bilateral, wide-spread, mechanical pain sensitivity in children with frequent episodic tension-type headache suggesting impairment in central nociceptive processing. Cephalalgia 2010;30:1049-1055.

[35] Fernandez-Mayoralas DM, Fernandez-de-las-Penas C, Ortega-Santiago R, Ambite-Quesada S, Jimenez-Garcia R, Fernandez-Jaen A. Generalized mechanical nerve pain hypersensitivity in children with episodic tension-type headache. Pediatrics 2010;126:e187; e194.

[36] Feuerstein M, Barr RG, Francoeur TE. Potential biobehavioral mechanisms of recurrent abdominal pain in children. Pain 1982;13:287-298.

[37] Fillingim RB, King CD, Ribeiro-Dasilva MC, Rahim-Williams B, Riley JL,3rd. Sex, gender, and pain: a review of recent clinical and experimental findings. J Pain 2009;10:447-485.

[38] Foster RL, Yucha CB, Zuk J, Vojir CP. Physiologic correlates of comfort in healthy children. Pain Manag Nurs 2003;4:23-30.

[39] Goffaux P, Lafrenaye S, Morin M, Patural H, Demers G, Marchand S. Preterm births: Can neonatal pain alter the development of endogenous gating systems? Eur J Pain 2008;12:945-951.

[40] Goodman JE, McGrath PJ. Mothers' modeling influences children's pain during a cold pressor task. Pain 2003;104:559-565.

[41] Goubert L, Vervoort T, Cano A, Crombez G. Catastrophizing about their children's pain is related to higher parent-child congruency in pain ratings: An experimental investigation. Eur J Pain 2009;13:196-201.

[42] Greenspan JD, Craft RM, LeResche L, Arendt-Nielsen L, Berkley KJ, Fillingim RB, Gold MS, Holdcroft A, Lautenbacher S, Mayer EA, Mogil JS, Murphy AZ, Traub RJ. Studying sex and gender differences in pain and analgesia: A consensus report. Pain 2007;132:S26-S45.

[43] Gupta S, McCarson KE, Welch KMA, Berman NEJ. Mechanisms of pain modulation by sex hormones in migraine. Headache: The Journal of Head and Face Pain 2011;51:905-922.

[44] Haas K, Lu Q, Evans S, Tsao JC, Zeltzer LK. Relationship between resting blood pressure and laboratory-induced pain among healthy children. Gend Med 2011;8:388-398.

[45] Han TI, Hong CZ, Kuo FC, Hsieh YL, Chou LW, Kao MJ. Mechanical pain sensitivity of deep tissues in children--possible development of myofascial trigger points in children. BMC Musculoskelet Disord 2012;13:13-2474-13-13.

[46] Hermann C, Hohmeister J, Demirakca S, Zohsel K, Flor H. Long-term alteration of pain sensitivity in school-aged children with early pain experiences. Pain 2006;125:278-285.

[47] Hicks CL, Baeyer CLv, Spafford PA, van Korlaar I, Goodenough B. The Faces Pain Scale – Revised: toward a common metric in pediatric pain measurement. Pain 2001;93:173-183.

[48] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. : The Cochrane Collaboration, 2011.

[49] Hirschfeld G, Zernikow B, Kraemer N, Hechler T, Aksu F, Krumova E, Maier C, Magerl W, Blankenburg M. Development of somatosensory perception in children: a longitudinal QST-study. Neuropediatrics 2012;43:10-16.

[50] Hogeweg JA, Kuis JW, Huygen ACJ, De Jong-de Vos van Steenwijk, Bernards ATM, Oostendorp RAB, Helders PJM. The pain threshold in juvenile chronic arthritis. Br J Rheumatol 1995;34:61-67.

[51] Hogeweg JA, Kuis W, Oostendorp RAB, Helders PJM. The influence of site of stimulation, age, and gender on pain threshold in healthy children. Phys Ther 1996;76:1331-1339.

[52] Hohmeister J, Demirakca S, Zohsel K, Flor H, Hermann C. Responses to pain in school-aged children with experience in a neonatal intensive care unit: Cognitive aspects and maternal influences. Eur J Pain 2009;13:94-101.

[53] Hohmeister J, Kroll A, Wollgarten-Hadamek I, Zohsel K, Demiraka S, Flor H, Hermann C. Cerebral processing of pain in school-aged children with neonatal nociceptive input: An exploratory fMRI study. Pain 2010;150:257-267.

[54] Jaaniste T, Hayes B, von Baeyer CL. Effects of preparatory information and distraction on children's cold-pressor pain outcomes: A randomized controlled trial. Behav Res Ther 2007;45:2789-2799.

[55] Keogh E. Sex differences in pain across the life course. In: Moore RJ. Handbook of Pain and Palliative Care: Biobehavioral Approaches for the Life Course. New York: Springer, 2012. pp. 347-366.

[56] Keogh E, Hatton K, Ellery D. Avoidance versus focused attention and the perception of pain: Differential effects for men and women. Pain 2000;85:225-230.

[57] Kessler RC, Avenevoli S, Merikangas KR. Mood disorders in children and adolescents: An epidemiologic perspective. Biol Psychiatry 2001;49:1002-1014.

[58] King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, MacDonald AJ. The epidemiology of chronic pain in children and adolescents revisited: A systematic review. Pain 2011;152:2729-2738.

[59] Larochette A-, Chambers CT, Craig KD. Genuine, suppressed and faked facial expressions of pain in children. Pain 2006;126:64-71.

[60] Law EF, Dahlquist LM, Sil S, Weiss KE, Herbert LJ, Wohlheiter K, Horn SB. Videogame distraction using virtual reality technology for children experiencing cold pressor pain: the role of cognitive processing. J Pediatr Psychol 2011;36:84-94.

[61] LeBaron S, Zeltzer L, Fanurik D. An investigation of cold pressor pain in children (part I). Pain 1989;37:161-171.

[62] LeResche L, Mancl LA, Drangsholt MT, Saunders K, Von Korff M. Relationship of pain and symptoms to pubertal development in adolescents. Pain 2005;118:201-209.

[63] Lu Q, Tsao JCI, Myers CD, Kim SC, Zeltzer LK. Coping Predictors of Children's Laboratory-Induced Pain Tolerance, Intensity, and Unpleasantness. J Pain 2007;8:708-717.

[64] Lu Q, Zeltzer LK, Tsao JCI, Kim SC, Turk N, Naliboff BD. Heart rate mediation of sex differences in pain tolerance in children. Pain 2005;118:185-193.

[65] McGrath PA, de Verber LL, Hearn MT. Multidimensional pain assessment in children. In: Fields HL, Dubner R, Cervero F. Advances in pain research and therapy. Proceedings of the 4th World Congress on Pain, vol. 9. New York: Raven, 1985. pp. 387-393.

[66] McGrath PA, Seifert CE, Speechley KN, Booth JC, Stitt L, Gibson MC. A new analogue scale for assessing children's pain: An initial validation study. Pain 1996;64:435-443.

[67] McMurtry CM, Noel M, Chambers CT, McGrath PJ. Children's fear during procedural pain: Preliminary investigation of the Children's Fear Scale. Health Psychology 2011;30:780-788.

[68] Meh D, Denislic M. Subclinical neuropathy in type I diabetic children. Electroencephalogr Clin Neurophysiol 1998;109:274-280.

[69] Meier PM, Berde CB, DiCanzio J, Zurakowski D, Sethna NF. Quantitative assessment of cutaneous thermal and vibration sensation and thermal pain detection thresholds in healthy children and adolescents. Muscle Nerve 2001;24:1339-1345.

[70] Mennella JA, Pepino MY, Lehmann-Castor SM, Yourshaw LM. Sweet preferences and analgesia during childhood: effects of family history of alcoholism and depression. Addiction 2010;105:666-675.

[71] Metsahonkala L, Anttila P, Laimi K, Aromaa M, Helenius H, Mikkelsson M, Jappila E, Viander S, Sillanpaa M, Salminen J. Extracephalic tenderness and pressure pain threshold in children with headache. Eur J Pain 2006;10:581-585.

[72] Miller A, Barr RG, Young SN. The cold pressor test in children: Methodological aspects and the analgesic effect of intraoral sucrose. Pain 1994;56:175-183.

[73] Mogil JS. Sex differences in pain and pain inhibition: Multiple explanations of a controversial phenomenon. Nature Reviews Neuroscience 2012;13:859-866.

[74] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Medicine 2009;6:e1000097.

[75] Moon EC, Chambers CT, Larochette A-, Hayton K, Craig KD, McGrath PJ. Sex differences in parent and child pain ratings during an experimental child pain task. Pain Res Manage 2008;13:225-230.

[76] Moon EC, Chambers CT, McGrath PJ. "He says, she says": A comparison of fathers' and mothers' verbal behavior during child cold pressor pain. J Pain 2011;12:1174-1181.

[77] Moon EC, Unruh AM. The effects of sex and gender on child and adolescent pain. In: McGrath PJ, Walker SM, Stevens BJ, Zempsky WT. Oxford Textbook of Paediatric Pain. Oxford, UK: Oxford University Press, 2014.

[78] Myers CD, Tsao JCI, Glover DA, Kim SC, Turk N, Zeltzer LK. Sex, Gender, and Age: Contributions to Laboratory Pain Responding in Children and Adolescents. J Pain 2006;7:556-564.

[79] Myers CD, Riley JL, Robinson ME. Psychosocial contributions to sex-correlated differences in pain. The Clinical Journal of Pain 2003;19:225-232.

[80] Niesters M, Dahan A, Kest B, Zacny J, Stijnen T, Aarts L, Sarton E. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. Pain 2010;151:61-68.

[81] Noel M, Chambers CT, McGrath PJ, Klein RM, Stewart SH. The influence of children's pain memories on subsequent pain experience. Pain 2012;153:1563-1572.

[82] Noel M, Chambers CT, McGrath PJ, Klein RM, Stewart SH. The Role of State Anxiety in Children's Memories for Pain. J Pediatr Psychol 2012;37:567-579.

[83] Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends, and changes after migration. Endocr Rev 2003;24:668-693.

[84] Piira T, Hayes B, Goodenough B, von Baeyer CL. Effects of attentional direction, age, and coping style on cold-pressor pain in children. Behav Res Ther 2006;44:835-848.

[85] Piira T, Taplin JE, Goodenough B, Von Baeyer CL. Cognitive-behavioural predictors of children's tolerance of laboratory-induced pain: Implications for clinical assessment and future directions. Behav Res Ther 2002;40:571-584.

[86] Popescu A, LeResche L, Truelove EL, Drangsholt MT. Gender differences in pain modulation by diffuse noxious inhibitory controls: A systematic review. Pain 2010;150:309-318.

[87] Racine M, Tousignant-Laflamme Y, Kloda LA, Dion D, Dupuis G, Choinière M. A systematic literature review of 10years of research on sex/gender and experimental pain perception–Part 1: Are there really differences between women and men? Pain 2011.

[88] Riley JLI,II, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: A meta-analysis. Pain 1998;74:181-187.

[89] Schmelzle-Lubiecki B, Campbell KAA, Howard RH, Franck L, Fitzgerald M. Long-term consequences of early infant injury and trauma upon somatosensory processing. European Journal of Pain 2007;11:799-809.

[90] Schmitz A, Vierhaus M, Lohaus A. Pain tolerance in children and adolescents: Sex differences and psychosocial influences on pain threshold and endurance. European Journal of Pain 2013;17:124-131.

[91] Smith MS, Martin-Herz SP, Womack WM, McMahon RJ. Recurrent headache in adolescents: Nonreferred versus clinic population. Headache 1999;39:616-624.

[92] Stuber M, Hilber SD, Mintzer LL, Castaneda M, Glover D, Zeltzer L. Laughter, Humor and Pain Perception in Children: A Pilot Study. Evid -Based Complement Altern Med 2009;6:271-276.

[93] Thastum M, Zachariae R, Scheler M, Bjerring P, Herlin T. Cold pressor pain: comparing responses of juvenile arthritis patients and their parents. Scand J Rheumatol 1997;26:272-279.

[94] Thastum M, Zachariae R, Herlin T. Pain experience and pain coping strategies in children with juvenile idiopathic arthritis. J Rheumatol 2001;28:1091-1098.

[95] The Cochrane Collaboration. Review Manager (RevMan). 2012.

[96] Trapanotto M, Pozziani G, Perissinotto E, Barbieri S, Zacchello F, Benini F. The cold pressor test for the pediatric population: Refinement of procedures, development of norms, and study of psychological variables. J Pediatr Psychol 2009;34:749-759.

[97] Tsao JCI, Evans S, Seidman LC, Zeltzer LK. Experimental pain responses in children with chronic pain and healthy children: How do they differ? Pain Res Manag 2012:103-109.

[98] Tsao JCI, Fanurik D, Zeltzer LK. Long-term effects of a brief distraction intervention on children's laboratory pain reactivity. Behav Modif 2003;27:217-232.

[99] Tsao JCI, Glover DA, Bursch B, Ifekwunigwe M, Zeltzer LK. Laboratory pain reactivity and gender: Relationship to school nurse visits and school absences. J Dev Behav Pediatr 2002;23:217-224.

[100] Tsao JCI, Lu Q, Kim SC, Zeltzer LK. Relationships among anxious symptomatology, anxiety sensitivity and laboratory pain responsivity in children. Cogn Behav Ther 2006;35:207-215.

[101] Tsao JCI, Lu Q, Myers CD, Kim SC, Turk N, Zeltzer LK. Parent and Child Anxiety Sensitivity: Relationship to Children's Experimental Pain Responsivity. J Pain 2006;7:319-326.

[102] Tsao JCI, Myers CD, Craske MG, Bursch B, Kim SC, Zeltzer LK. Role of Anticipatory Anxiety and Anxiety Sensitivity in Children's and Adolescents' Laboratory Pain Responses. J Pediatr Psychol 2004;29:379-388.

[103] Vederhus BJ, Eide GE, Natvig GK, Markestad T, Graue M, Halvorsen T. Pain tolerance and pain perception in adolescents born extremely preterm. J PAIN 2012;13:978-987.

[104] Verhoeven K, Goubert L, Jaaniste T, Van Ryckeghem, D. M. L., Crombez G. Pain catastrophizing influences the use and the effectiveness of distraction in school children. European Journal of Pain 2012;16:256-267.

[105] Vervoort T, Caes L, Trost Z, Sullivan M, Vangronsveld K, Goubert L. Social modulation of facial pain display in high-catastrophizing children: An observational study in schoolchildren and their parents. Pain 2011;152:1591-1599.

[106] Vervoort T, Goubert L, Crombez G. The relationship between high catastrophizing children's facial display of pain and parental judgment of their child's pain. Pain 2009;142:142-148.

[107] Vervoort T, Goubert L, Eccleston C, Verhoeven K, De Clercq A, Buysse A, Crombez G. The effects of parental presence upon the facial expression of pain: The moderating role of child pain catastrophizing. Pain 2008;138:277-285.

[108] Vervoort T, Caes L, Trost Z, Notebaert L, Goubert L. Parental attention to their child's pain is modulated by threat-value of pain. Health Psychology 2012;31:623-631.

[109] Vierhaus M, Lohaus A, Schmitz A-. Sex, gender, coping, and self-efficacy: Mediation of sex differences in pain perception in children and adolescents. Eur J Pain 2011;15:621.e1; 621.e8.

[110] Walker LS, Williams SE, Smith CA, Garber J, Van Slyke DA, Lipani T, Greene JW, Mertz H, Naliboff BD. Validation of a symptom provocation test for laboratory studies of abdominal pain and discomfort in children and adolescents. J Pediatr Psychol 2006;31:703-713.

[111] Walker SM, Franck LS, Fitzgerald M, Myles J, Stocks J, Marlow N. Long-term impact of neonatal intensive care and surgery on somatosensory perception in children born extremely preterm. Pain 2009;141:79-87.

[112] Weidenbacker R, Sandry M, Moed G. Sensory discrimination of chidlren with cerebral palsy: Pressure/pain thresholds on the foot. Percept Mot Skills 1963;17:603-610.

[113] Weiss KE, Dahlquist LM, Wohlheiter K. The effects of interactive and passive distraction on cold pressor pain in preschool-aged children. J Pediatr Psychol 2011;36:816-826.

[114] Wollgarten-Hadamek I, Hohmeister J, Demirakça S, Zohsel K, Flor H, Hermann C. Do burn injuries during infancy affect pain and sensory sensitivity in later childhood? Pain 2009;141:165-172.

[115] Wollgarten-Hadamek I, Hohmeister J, Zohsel K, Flor H, Hermann C. Do school-aged children with burn injuries during infancy show stress-induced activation of pain inhibitory mechanisms? European Journal of Pain 2011;15:e1-e10.

[116] World Health Organization. What do we mean by "sex" and "gender"? 2012;2012.

[117] Zeltzer LK, Fanurik D, LeBaron S. The cold pressor pain paradigm in children: Feasibility of an intervention model (part II). Pain 1989;37:305-313.

[118] Zohsel K, Hohmeister J, Oelkers-Ax R, Flor H, Hermann C. Quantitative sensory testing in children with migraine: Preliminary evidence for enhanced sensitivity to painful stimuli especially in girls. Pain 2006;123:10-18.

*Summary

Boerner et al. 25 word summary for ‘Sex differences in experimental pain among healthy children: A systematic review and meta-analysis

Meta-analysis found that girls had increased pain intensity on the cold pressor task, and lower pain tolerance and threshold in response to heat pain.

Figure

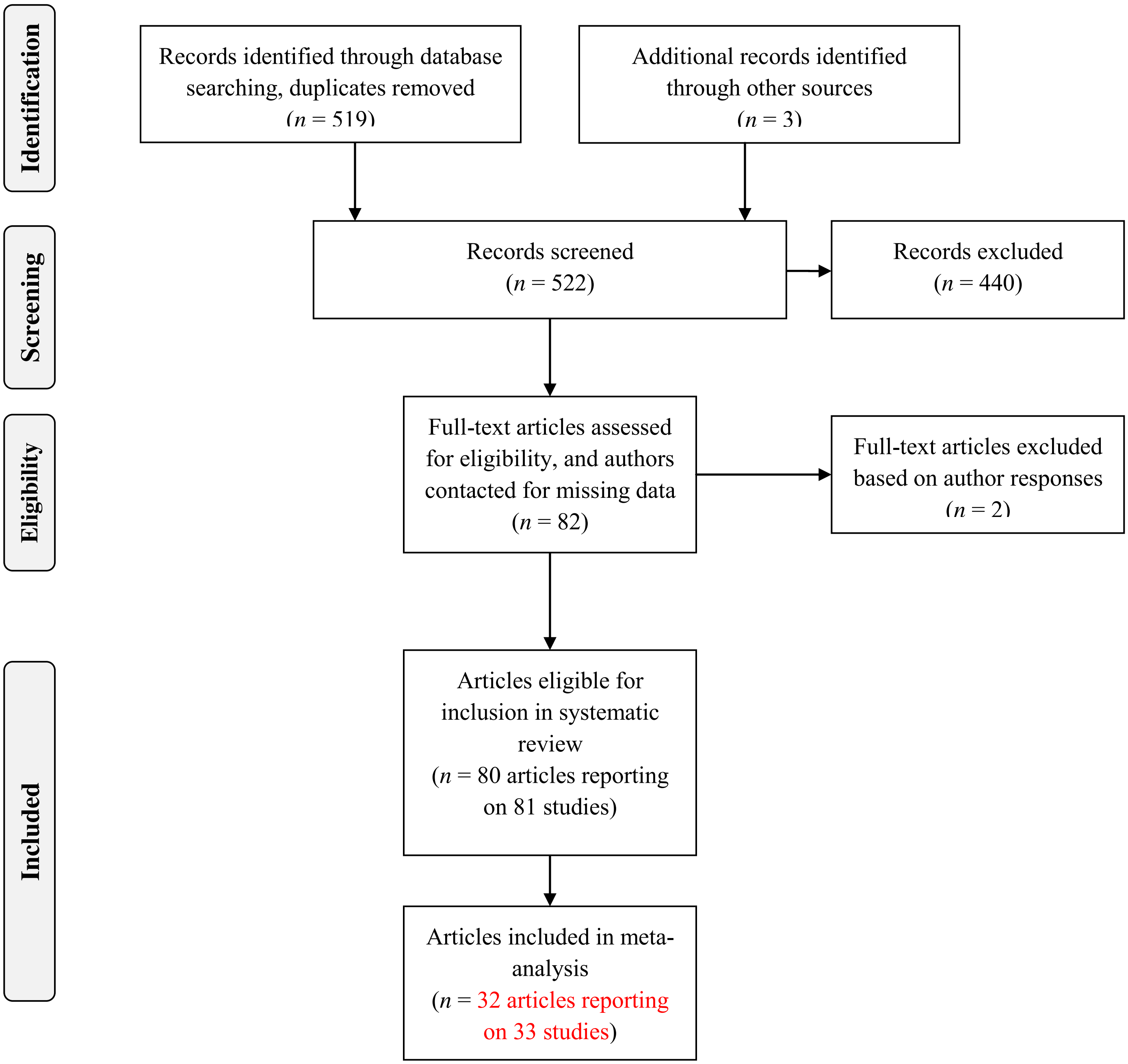

Figure 1. PRISMA flow diagram of the process of identification and screening of articles for inclusion in the systematic review and meta-analysis.

Table

Table 1. Studies examining sex differences in experimental cold pain.

Authors	Sample Size		Mean age (range)	Method (location)	Pain outcomes					
	Boys	Girls			Intensity	Threshold	Tolerance	Affect	Facial activity	Physiological responses
Allen et al. 2009[a][3]	119	116	12.7 (8-18)	CPT (dominant hand)						G=B
Blankenburg et al. 2010 [8]	88	88	NR (6-16)	QST cold pain threshold (face, hand, foot)		G<B				
Blankenburg et al. 2011[b][9]	88	85	NR (7-14)	QST cold pain threshold (hands)		G=B				
Chambers et al. 2002[16]	60	60	9.74 (8-12)	CPT (left hand)	G=B		G=B	G=B	G<B	G=B
Coldwell et al. 2002[20]	38	37	9.7 (8-11)	CPT (right forearm)	G=B					
Foster et al. 2003[38]	53	47	12.43 (8-17)	CPT (left hand)						G=B and G<B[c]
Goodman et	48	48	12.6	CPT	G=B	G=B	G=B		G=B	

al. 2003[40]			(10-14)	(non-dominant hand)						
Jaaniste et al. 2007[54]	38	41	9.16 (7-12)	CPT (non-dominant arm)	G=B		G=B			
Larochette et al. 2006[59]	25	25	9.74 (8-12)	CPT (arms)					G=B	
LeBaron et al. 1989[d][61]	19	18	NR (6-12)	CPT (arms)			G=B	G>B		
Miller et al. 1994[72]	23	21	NR (8-11)	CPT (non-dominant forearm)			G>B			
Moon et al. 2008[75]	37	36	8.04 (4-12)	CPT (hand)	G=B				G=B	G=B
Myers et al. 2006[a][78]	120	120	12.7 (8-18)	CPT (non-dominant hand)	G=B		G=B	G=B		
Piira et al. 2002[85]	22	31	9.08 (7-14)	CPT (dominant arm)			G=B			
Piira et al.	55	65	10.16	CPT	G=B		G=B			

2006[84]			(7-14)	(non-dominant arm)					
Trapanotto et al. 2009 [96]	78	63	10.1 (8-12)	CPT (non-dominant arm)	G=B	G=B	G=B	G=B	
Tsao et al. 2002[d][99]	19	32	NR (8-10)	CPT (arms)	G=B		G=B		
Verhoeven et al. 2012[e][104]	39	42	13.6 (9-18)	CPT (left hand)				G=B	
Vervoort et al. 2009[f][106]	32	30	12.46 (9-15)	CPT (left hand)					G=B
Vervoort et al. 2011[e] [105]	22	16	14.5 (10-18)	CPT (hands)	G=B				G<B
Vierhaus et al. 2011[109] (Study #1)	53	65	12.74 (10-17)	CPT (non-dominant forearm)	G>B		G=B		
Vierhaus et al. 2011[109] (Study #2)	81	67	12.8 (10-17)	CPT (non-dominant forearm)	G>B		G=B		

Weiss et al. 2011[113]	31	30	4.21 (3-5)	CPT (non-dominant hand)			G=B	
Zeltzer et al. 1989[g][117]	NR	NR	NR (6-12)	CPT (arms)			G>B	G>B

NOTE. In the case of studies with overlapping samples, only the first published account to meet review inclusion criteria is included. Note that while higher ratings on pain intensity indicate greater pain sensitivity, lower levels of threshold and tolerance indicate greater pain sensitivity. NR = not reported.

The following studies using experimental cold pain were included in the systematic review but did not report the results of statistical tests of sex differences in healthy children in the published manuscript: [6,23-26,36,39,60,68-70,76,81,82,91-94]

[a] Evans et al. 2008 [29], Evans et al. 2008 [31], Evans et al. 2009 [30], Haas et al. 2011 [44], Lu et al. 2007 [63], Tsao et al. 2004 [102], Tsao et al. 2006 [100], Tsao et al. 2006 [101], and Tsao et al. 2012 [97] reported on results of the cold pressor task with the same sample of children.

[b] Hirschfeld et al. 2012 [49] reported on results of a cold pain threshold test re-testing the same sample of children.

[c] No sex differences were found on the majority of physiological outcomes in response to pain (heart rate, skin conductance, respiratory rate, EMG, or skin temperature), but boys had significantly higher blood pressure than girls.

[d] Fanurik et al. 1993 [32] and Tsao et al. 2003 [98] reported on results of the cold pressor task with the same sample of children.

[e] Studies reported on results from the same sample of children.

[f] Caes et al. 2011 [12] reported on results of the cold pressor task with the same sample of children.

[g] LeBaron et al. 1989 [61] reported on results of the cold pressor task with the same sample of children.

Table

Table 2. Studies examining sex differences in experimental heat pain.

Authors	Sample Size		Mean age (range)	Location	Pain outcomes					
	Boys	Girls			Intensity	Threshold	Tolerance	Affect	Facial activity	Physiological responses
Allen et al. 2009[a] [3]	119	116	12.7 (8-18)	Forearms						G=B
Blankenburg et al. 2010 [8]	88	88	NR (6-16)	Face, hand, foot		G<B				
Blankenburg et al. 2011[b] [9]	88	85	NR (7-14)	Hands		G<B				
Lu et al. 2005[a] [64]	120	124	12.73 (8-18)	Forearms			G=B			
Myers et al. 2006[a] [78]	120	120	12.7 (8-18)	Forearms	G=B			G=B		
Vervoort et al. 2012 [108]	32	30	13.08 (11-15)	Right wrist	G=B		G<B		G=B	

NOTE. In the case of studies with overlapping samples, only the first published account to meet review inclusion criteria is included. Note that while higher ratings on pain intensity indicate greater pain sensitivity, lower levels of threshold and tolerance indicate greater pain sensitivity. NR = not reported.

The following studies using experimental heat pain were included in the systematic review but did not report the results of statistical tests of sex differences in healthy children in the published manuscript:[6,13,39,46,52,53,68,69,114,115]

[a] Evans et al. 2008 [29], Evans et al. 2008 [31], Evans et al. 2009 [30], Haas et al. 2011 [44], Lu et al. 2007 [63], Tsao et al. 2004 [102], Tsao et al. 2006 [100], Tsao et al. 2006 [101], and Tsao et al. 2012 [97] reported on results of the cold pressor task with the same sample of children.

[b] Hirschfeld et al. 2012 [49] reported on results of a heat pain threshold test re-testing the same sample of children.

Table

Table 3. Studies examining sex differences in experimental pressure pain.

Authors	Sample Size		Mean age (range)	Location	Pain outcomes					
	Boys	Girls			Intensity	Threshold	Tolerance	Affect	Facial activity	Physiological responses
Allen et al. 2009[a][3]	119	116	12.7 (8-18)	Fingers						G=B
Blankenburg et al. 2010[8]	88	88	NR (6-16)	Face, hand, foot		G<B				
Blankenburg et al. 201[b][9]	88	85	NR (7-14)	Hands		G=B				
Chaves et al. 2007[c] [17]	9	7	8.33 boys and 8.71 girls (7-12)	Face, hand		G=B				
Han et al. 2012[45]	258	247	7.9 (4-11)	Forearm		G=B				
Hogeweg et al. 1995[50]	33	36	11.5 boys and 11.5 girls (6-17)	Joints of the elbow, wrist, knee, and ankle, and paraspinally		G=B				
Hogeweg et al.	33	36	11.4	Joints of the		G=B[d]				

1996[51]			(6-17)	elbow, wrist, knee, and ankle, and paraspinally					
Metsahonkala et al. 2006[71]	22	37	NR (13)	Five cranial and neck-shoulder points and three extracephalic points		G<B			
Myers et al. 2006[a][78]	120	120	12.7 (8-18)	Fingers	G=B			G=B	
Tsao et al. 2004[a][102]	60	58	12.6 (8-18)	Fingers			G<B		
Vervoort et al. 2008[e][107]	40	44	11.82 (9-15)	Neck, shoulder	G=B and G>B [f]				G=B

NOTE. In the case of studies with overlapping samples, only the first published account to meet review inclusion criteria is included. Note that while higher ratings on pain intensity indicate greater pain sensitivity, lower levels of threshold and tolerance indicate greater pain sensitivity. NR = not reported.

The following studies using experimental pressure pain were included in the systematic review but did not report the results of statistical tests of sex differences in healthy children in the published manuscript:[2,5,18,33-35,112,115]

[a] Evans et al. 2008 [29], Evans et al. 2009 [30], Evans et al. 2008 [31], Haas et al. 2011 [44], Lu et al. 2007 [63], Lu et al. 2005[64], Tsao et al. 2012 [97], Tsao et al. 2006 [100], and Tsao et al. 2006 [101] reported on results of the cold pressor task with the same sample of children.

[b] Hirschfeld et al. 2012 [49] reported on results of the pressure pain threshold test re-testing the same sample of children.

[c] Note that this sample conducted sex difference statistics combining both the healthy control group and the clinical sample (mean age is presented for healthy sample only).

[d] This study reported that there were no significant sex differences except for at the knee in ages 12-17 years, where G<B.
[e] Goubert et al. 2009 [41] reported on results of the pressure pain threshold test with the same sample of children.
[f] Note that while no sex differences were present during the pressure pain threshold test phase (which was the result included in the systematic review, as it was the first trial of the pressure pain task), in the experimental phase girls reported a significantly higher pain intensity than boys.

Table

Table 4. Studies examining sex differences in other experimental pain tasks.

Pain task	Authors	Sample Size		Mean age (range)	Location	Pain outcomes	
		Boys	Girls			Intensity	Threshold
Mechanical pain							
	Bar-Shalita et al. 2009[6]	18	16	7.75 (NR)	Forearm	G=B [a]	
	Blankenburg et al. 2010[8]	88	88	NR (6-16)	Face, hand, foot	G=B	G=B
	Blankeburg et al. 2011[b] [9]	88	85	NR (7-14)	Hands	G=B	G=B
Wind-up ratio							
	Blankenburg et al. 2010[8]	88	88	NR (6-16)	Face, hand, foot	G=B	
	Blankenburg et al. 2011[b] [9]	88	85	NR (7-14)	Hands		G=B
Water load task							
	Walker et al. 2006[110]	60	60	11.46 (8-15)	Abdomen	G=B [c]	

NOTE. In the case of studies with overlapping samples, only the first published account to meet review inclusion criteria is included. Note that while higher ratings on pain intensity indicate greater pain sensitivity, lower levels of threshold indicate greater pain sensitivity. Note that columns for pain tolerance, pain affect, facial activity in response to pain, and physiological responses to pain are not included in the present table, as none of these outcomes were measured for the listed pain tasks. NR = not reported.

The following studies using experimental mechanical pain were included in the systematic review but did not report the results of statistical tests of sex differences in healthy children in the published manuscript:[46,114,118]

[a] Note that this sample conducted sex difference statistics combining both the healthy control group and the clinical sample (mean age is presented for healthy sample only).

[b] Hirschfeld et al. 2012 [49] reported on results of a mechanical pain threshold test and wind-up ratio re-testing the same sample of children.

[c] Combined abdominal pain/discomfort score.